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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,273	01/18/2001	Michael Bittner	22564-0707	1332

20855 7590 08/04/2006

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EXAMINER	
CROW, ROBERT THOMAS	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 08/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	09/766,273	BITTNER ET AL.	
	Examiner	**Art Unit**	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 22 May 2006.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-44 is/are pending in the application.

4a) Of the above claim(s) 39-43 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-38 and 44 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 18 January 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 09766273.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

Amendment

The Amendment filed 22 May 2006 is acknowledged and entered.

Election/Restrictions

1. Applicant's original election without traverse of Group I in the reply filed on 29 May 2001 is acknowledged.

2. Claims 39-43 have been withdrawn. Claims 1-38 and 44 are currently under prosecution.

Claim Objections

Claim 30 is objected to because of the following informalities: claim 30 recites limitation "which may the same as" in line 6 of the claim. This appears to be a typographical error. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 30 is indefinite in the following recitations:

A. The limitation "the first tag-binding polynucleotide can bind to the second tag sequence" in lines 14-15 of the claim. It is unclear how the second tag-binding conjugate can bind to the second tag sequence when the <u>first</u> tag-binding polynucleotide (emphasis added by the examiner) can bind to the second tag sequence. It is suggested that the claim be amended to clearly indicate which sequences are bound to which tags.

B. The limitation "the semiconductor nanocrystal" in the last line of the claim. It is unclear if "the semiconductor nanocrystal" includes "the first semiconductor nanocrystal" of

independent claim 1. It is suggested that each semiconductor nanocrystal be designated first, second, etc.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-5, 14-15, 17, 19, 24-25, 28, 30-32, and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998).

Regarding claim 1, Mirkin et al teach a method for assaying a first sample for a first probe comprising:

providing a substrate attached to a first target (e.g., a glass slide having an oligonucleotide attached; Example 10, pages 81-84 and Figure 13A);

contacting the substrate with the first sample, wherein the first sample is suspected of comprising the first probe (e.g., analyte DNA is added, Figure 13A), wherein the first probe comprises a first probe polynucleotide comprising a first tag sequence which does not bind to the first target and a first binding sequence which does bind to the first target, and wherein contacting the substrate with the first sample takes place under conditions in which the first binding sequence can bind to the first target (e.g., analyte DNA is hybridized onto the substrate [Figure 13A], wherein the analyte DNA is a linking oligonucleotide having a 12 base pair end that is complementary to the attached oligonucleotide and also has a 12 base pair overhang; page 83, lines 1-10 and Figure 13A);

contacting the first sample with a first tag-binding conjugate wherein said first tag-binding conjugate comprises a first semiconductor nanocrystal conjugated to a first tag-binding polynucleotide (e.g., an oligonucleotide complementary to the overhang of the linking oligonucleotide and having a nanoparticle attached [page 83, lines 10-20], wherein the nanoparticle is a semiconductor nanoparticle; page 19, lines 24-34),

wherein the first tag-binding polynucleotide can bind to the first tag sequence but not the first target (e.g., the nanoparticle-attached oligonucleotide binds the overhang; page 83, lines 10-20),

and wherein contacting the first sample with the first tag-binding conjugate takes place under conditions in which the first tag-binding polynucleotide can bind to the first tag sequence (e.g., hybridization occurs; page 83, lines 10-20 and Figure 13A); and

determining if the first semiconductor nanocrystal is associated with the substrate (e.g., color changes on the substrate are noted; page 83, lines 18-20 and Figure 13A, last step).

Regarding claim 2, Mirkin et al teach the method of claim 1, wherein the substrate is a slide (e.g., a glass slide; page 82, lines 30-34).

Regarding claim 3, Mirkin et al teach the method of claim 1, wherein the substrate comprises a plurality of different targets (e.g., the substrate has rows of spots, each spot containing a different type of oligonucleotide; page 41, lines 2-11).

Regarding claim 4, Mirkin et al teach the method of claim 3, wherein the substrate comprises a microarray (page 40, lines 32-35).

Regarding claim 5, Mirkin et al teach the method of claim 1, wherein the first probe polynucleotide is produced from an amplification process comprising a polymerase chain reaction (e.g., the nucleic acid being detected in a polymerase chain reaction [i.e., PCR] solution; page 24, lines 18-24).

Regarding claims 14 and 15, Mirkin et al teach the method of claim 1, wherein the first tag sequence is located at or nearer either the 5' end of the 3' end of the first probe polynucleotide (e.g., oligonucleotides are functionalized for attachment to solid surfaces at either their 3' termini or their 5' termini; page 21, line 34-page 22, line 22).

Mirkin et al teach the attachment of oligo-nucleotides occurs at either the 3' end or the 5' end. The end that is attached dictates which end is the overhang of the linking oligonucleotide [i.e., the first tag sequence] will be on; i.e., if the first target is attached to the slide on its 3' end, he first tag sequence will be on the 3' end of the probe. Because Mirkin et al teach attachment of the first target to the substrate at either end, and because the attachment end of the first target dictates which end the first tag is located on, Mirkin et al anticipate the location of the tag sequence at either end of the first probe polynucleotide.

Regarding claim 17, Mirkin et al teach the method of claim 1, wherein contacting the sample with the first target takes place prior to contacting the sample with the first tag-binding conjugate (e.g., Example 10).

Regarding claim 19, Mirkin et al teach the method of claim 1, wherein contacting the sample with the first target takes place simultaneously contacting the sample with the first tag-binding conjugate (e.g., Example 10). It is noted that during the final step of hybridization step of Example 10 (page 83, lines 10-20), both the sample (i.e., the linking oligonucleotide) and the first tag-binding conjugate (e.g., the complementary oligonucleotide attached to the semiconductor nanoparticle) are both present; therefore, the contacting of the sample with the first target and the first tag-binding conjugate is occurring simultaneously.

Regarding claims 24 and 25, Mirkin et al teach the method of claim 1, wherein the first semiconductor nanocrystal comprises a core of CdSe (page 19, lines 24-26).

Regarding claim 28, Mirkin et al teach the method of claim 1, wherein the sample is assayed to determine if the probe is present in the sample (e.g., the method detects nucleic acids; Abstract).

Regarding claim 30, Mirkin et al teach the method of claim 1, further comprising

assaying a sample, which is the first sample (i.e., the first sample of claim 1; Figure 13A), for a second probe comprising contacting the substrate with the sample (e.g., another molecule of the first probe of claim 1 contacts the substrate; page 83, lines 1-10 and Figure 13A),

wherein the substrate comprises a target which is the first target (i.e., the first target of claim 1; page 83, lines 1-10 and Figure 13A), wherein the sample is suspected of comprising the second probe (i.e., another molecule of the first probe of claim 1; page 83, lines 1-10 and Figure 13A),

wherein the second probe comprises a second probe polynucleotide comprising a second tag sequence which does not bind the target (i.e., another molecule of first probe of claim 1; page 83, lines 1-10 and Figure 13A) and a second binding sequence, which is the same as the first binding sequence, which does bind the target, and wherein contacting the substrate with the sample takes place under condition in which the second binding sequence can bind to the target (i.e., the conditions of claim 1; page 83, lines 1-10 and Figure 13A);

contacting the sample with a second tag-binding conjugate (i.e., another molecule of the first tag-binding conjugate), wherein said second tag-binding conjugate comprises a semiconductor nanocrystal which is different from the first semiconductor nanocrystal (i.e., a different nanocrystal particle composed of the same elements as the first nanocrystal particle; page 83, lines 10-20 and page 19, lines 24-34), conjugated to a second tag-binding polynucleotide (i.e., a second molecule of the first tag-binding polynucleotide; page 83, lines 10-20 and Figure 13A),

wherein the second tag-binding polynucleotide can bind to the second tag sequence but not to the target (i.e., because the **second** tag sequence binds to the **first** tag-binding polynucleotide as required in lines 14-15 of the instant claim, the second tag-binding polynucleotide has the same sequence as the first second tag-binding polynucleotide, and is therefore merely another molecule of the same polynucleotide; page 83, lines 10-20 and Figure 13A), and

wherein contacting the sample with the second tag-binding conjugate takes place under conditions in which the first tag-binding polynucleotide can bind to the second tag sequence (i.e., because the **first** tag-binding polynucleotide can bind the **second** tag sequence as required by the claim, the first probe and the second probe can have the same sequence; therefore, the second probe is broadly interpreted as being another molecule of the first probe; page 83, lines 10-20 and Figure 13A), and

determining if the semiconductor nanocrystal is associated with the substrate (i.e., the determining step of claim 1; page 83, lines 18-20 and Figure 13A, last step).

As stated above, the claim is interpreted to read:

a) the sample of claim 30 is the first sample of claim 1;

b) the target of claim 30 is the first target of claim 1;

c) the second probe polynucleotide binds the first binding sequence of claim 1 (i.e., the second and first binding sequences are the same);

d) the semiconductor nanocrystal of claim 30 is different from the first semiconductor nanocrystal (i.e., a different particle composed of the same elements);

e) the second tag-binding polynucleotide of claim 30 does not bind the target but does bind the second tag sequence; and

f) the **first** tag-binding polynucleotide binds the **second** tag sequence (i.e., the first tag-binding polynucleotide and the second tag-binding polynucleotide both bind the second tag sequence).

Using the above interpretation as required by the claim, the first and second probes both bind the same sequences, and are therefore interpreted as different molecules having the same sequence. Thus, the claim has been given the broadest reasonable interpretation consistent with the specification (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]).

Regarding claim 31, Mirkin et al teach the method of claim 1, wherein the substrate is washed (i.e., rinsed with buffer) prior to determining of the first semiconductor nanocrystal is associated with the first target (page 83, lines 10-20).

Regarding claim 32, Mirkin et al teach the method of claim 1, wherein a medium is added to the substrate to dilute the concentration of the first semiconductor nanocrystal prior to determining of the semiconductor nanocrystal is associated with the first target (e.g., the substrate is removed and rinsed with a buffer [page 83, lines 10-20]; i.e., after removal, the nanoparticles are at a concentration on the substrate, and the rinsing of the substrate, by introducing more fluid [but not more nanoparticles] to the substrate, thereby diluting the nanoparticles).

Regarding claim 44, Mirkin et al teach the method of claim 1, wherein the target is a polynucleotide is located in a cell, which may be fixed or unfixed (page 24, lines 18-20).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Pearson et al (U.S. Patent No. 5,916,779, issued 29 June 1999).

Regarding claim 6, Mirkin et al teach the method of claim 1 for assaying a first sample for a first probe comprising:

providing a substrate attached to a first target (e.g., a glass slide having an oligonucleotide attached; Example 10, pages 81-84 and Figure 13A);

contacting the substrate with the first sample, wherein the first sample is suspected of comprising the first probe (e.g., analyte DNA is added, Figure 13A), wherein the first probe comprises a first probe polynucleotide comprising a first tag sequence which does not bind to the first target and a first binding sequence which does bind to the first target, and wherein contacting the substrate with the first sample takes place under conditions in which the first

binding sequence can bind to the first target (e.g., analyte DNA is hybridized onto the substrate [Figure 13A], wherein the analyte DNA is a linking oligonucleotide having a 12 base pair end that is complementary to the attached oligonucleotide and also has a 12 base pair overhang; page 83, lines 1-10 and Figure 13A);

contacting the first sample with a first tag-binding conjugate wherein said first tag-binding conjugate comprises a first semiconductor nanocrystal conjugated to a first tag-binding polynucleotide (e.g., an oligonucleotide complementary to the overhang of the linking oligonucleotide and having a nanoparticle attached [page 83, lines 10-20], wherein the nanoparticle is a semiconductor nanoparticle; page 19, lines 24-34),

wherein the first tag-binding polynucleotide can bind to the first tag sequence but not the first target (e.g., the nanoparticle-attached oligonucleotide binds the overhang; page 83, lines 10-20),

and wherein contacting the first sample with the first tag-binding conjugate takes place under conditions in which the first tag-binding polynucleotide can bind to the first tag sequence (e.g., hybridization occurs; page 83, lines 10-20 and Figure 13A); and

determining if the first semiconductor nanocrystal is associated with the substrate (e.g., color changes on the substrate are noted; page 83, lines 18-20 and Figure 13A, last step).

While Mirkin et al teach amplification of the probe polynucleotide (page 24, lines 32-34), Mirkin et al are silent with respect to reverse transcriptase.

However, Pearson et al teach a method of amplifying polynucleotides by contacting the sample with reverse transcriptase under conditions that reverse transcribe RNA to DNA (Abstract) with the added benefit that amplification of RNA targets is useful for monitoring upregulation of cancer genes (column 2, lines 13-25).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising amplification as taught by

Mirkin et al with amplification using reverser transcriptase as taught by Pearson et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in amplification of RNA targets useful for monitoring upregulation of cancer genes as explicitly taught by Pearson et al (column 2, lines 13-25).

3. Claims 1 and 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Fischer (U.S. Patent No. 5,876,932, issued 2 March 1999).

Regarding claim 7, the method of claim 1 is discussed above. While Mirkin et al teach amplification of the probe polynucleotide (page 24, lines 32-34), Mirkin et al are silent with respect to primers.

However, Fischer teaches a method for assaying a sample for a probe (i.e., assaying for gene expression, Abstract) comprising incorporating the first tag sequence into the first probe polynucleotide by employing a first primer polynucleotide (e.g., the sequence being detected is amplified; Figure 1).

The support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed is discussed above. Because Fischer teaches producing the first probe polynucleotide through amplification employing a first primer (Figure 1), and because the first probe polynucleotide must contain the tag sequence as required by claim 1, the first primer must incorporate the tag sequence into to first probe polynucleotide (otherwise, the first primer would not direct the synthesis of the first probe polynucleotide).

Fischer also teaches the added benefit that the primer allows selective amplification of members of a gene family (column 2, lines 55-60).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising amplification as taught by Mirkin et al with the primers as taught by Fischer with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing selective amplification of members of a gene family as explicitly taught by Fischer (column 2, lines 55-60).

Regarding claim 8, the method of claim 7 is discussed above. Fischer also teaches the primer binds the polyadenlyated tail of mRNA (e.g., Figure 1, step 1; Figure 2, step 2; and column 4, lines 64-67).

Regarding claim 9, the method of claim 7 is discussed above. Fischer also teaches the primer binds to a plurality of different sequences (e.g., degenerate random primers are used; column 3, lines 25-39).

4. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) and Fischer (U.S. Patent No. 5,876,932, issued 2 March 1999) as applied to claim 9 above, and further in view of Caetano-Anolles (U.S. Patent No. 5,962,221, issued 5 October 1999).

Regarding claim 10, the method of claim 9 is discussed above. While Fischer teaches degenerate primers (column 3, lines 25-39), neither Mirkin et al nor Fischer teaches the four 3′ residues are degenerate.

However, Caetano-Anolles teaches primers (i.e., SSR primers) having degenerate 3′ ends of 4 residues (e.g., 2 to 10 nucleotides in length) with the added advantage of allowing detection of polymorphisms (column 3, lines 22-31). The instantly claimed 4 bases is an obvious variant the 2-10 nucleotides as taught by Caetano-Anolles.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising amplification with

degenerate primers as taught by Mirkin et al and Fischer with the 3′ degenerate primers as taught by Caetano-Anolles with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing detection of polymorphisms as explicitly taught by Caetano-Anolles (column 3, lines 22-31).

5. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) and Fischer (U.S. Patent No. 5,876,932, issued 2 March 1999) as applied to claim 9 above, and further in view Kambara et al (U.S. Patent No. 5,985,556, issued 16 November 1999).

Regarding claim 11, the method of claim 9 is discussed above. While Fischer teaches primers comprising bases that bind more than one base (e.g., inosine, column 3, lines 25-39), neither Mirkin et al nor Fischer teaches bases at the four 3′ residues are degenerate.

However, Kambara et al teach a method of detecting a first probe in a first sample (e.g., sequencing a DNA fragment; Abstract) comprising a primer having inosine at the fourth position of the 3′ end of a primer with the added advantage of enhancing selectivity (column 31, lines 15-30). The instantly claimed "bases at the four 3′ residues," which is broadly interpreted as being more than one base of the four 3′ bases, is therefore an obvious variant of the one inosine at the fourth position as taught by Kambara et al.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising amplification with degenerate primers as taught by Mirkin et al and Fischer with the bases that can base pair with more that one different base in the four 3′ residues as taught by Kambara et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a primer having inosine at the

fourth position of the 3' end of a primer with the added advantage of enhancing selectivity as explicitly taught by Kambara et al (column 31, lines 15-30).

6. Claims 1 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Hunkapiller et al (U.S. Patent No. 5,942,609, issued 24 August 1999).

Regarding claim 12, the method of claim 1 is discussed above. Mirkin et al do not teach ligation.

However, Hunkapiller et al teach a method of detection of poly-nucleotides on solid supports (Title) comprising the ligation of polynucleotide sequences into oligonucleotides (column 3, line 50-column 4, line 33) with the added advantage that ligation (i.e., using DNA ligase) provides a proof-reading advantage that produces the correct ligation product (column 5, lines 21-25).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Mirkin et al with the incorporation a sequence using a ligation as taught by Hunkapiller et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a proof-reading advantage that produces the correct ligation product as explicitly taught by Hunkapiller et al (column 5, lines 21-25).

7. Claims 1 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Agrawal et al (U.S. Patent No. 5,652,103, issued 29 July 1997).

Regarding claim 13, the method of claim 1 is discussed above. Mirkin et al do not teach terminal transferase.

However, Agrawal et al teach a method of detecting a first probe in a first sample (e.g., determining nucleotide sequences; Abstract) wherein poly-nucleotides sequences are incorporated into oligonucleotides using terminal transferase with the added benefit that terminal transferase provides an efficient and reliable method for producing a molecule of suitable length for sequencing (column 3, lines 8-15).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Mirkin et al with the incorporation a sequence using terminal transferase as taught by Agrawal et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in providing an efficient and reliable method for producing a molecule of suitable length for sequencing as explicitly taught by Agrawal et al (column 3, lines 8-15).

8. Claims 1 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Cleuziat et al (U.S. Patent No. 5,849,547, issued 15 December 1998).

Regarding claim 16, the method of claim 1 is discussed above. While Mirkin et al also teach the first probe comprises a base which is not selected from the group consisting of adenine, guanine, cytosine, thymine, and uracil (e.g., the linking oligonucleotide contains modified bases; page 23, lines 14-24). Mirkin et al does not specifically teach the tag sequence comprises a base other that A,G,T,C, and U (i.e., Mirkin et al does not teach hybridization of a probe to the modified base).

However, Cleuziat et al teach a method of detecting nucleic acids (e.g., amplifying target nucleic acids; Abstract) comprising hybridization to sequences containing modified bases with the added advantage that the resulting duplex exhibits greater stability (column 23, lines 29-34).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising hybridization of the first tag sequence as taught by Mirkin et al with hybridization to bases other that A, G, C, T, and U as taught by Cleuziat et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in the resulting duplex exhibiting greater stability as explicitly taught by Cleuziat et al (column 23, lines 29-34).

9. Claims 1 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998).

Regarding claim 18, the method of claim 1 is discussed above. Mirkin et al also teach the contacting of the sample with the first target takes place prior to contacting the sample with the first tag-binding conjugate (e.g., Example 10).

With respect to contacting the sample with the first target after contacting the sample with the first tag-binding conjugate, the courts have held that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results (*In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946). See MPEP 2144.04 IV.C. Because Mirkin et al teach all of the steps required in claim 18, the claim is obvious over Mirkin et al.

10. Claims 1 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Klinger et al (U.S. Patent No. 5,693,783, issued 2 December 1997).

Regarding claim 20, the method of claim 1 is discussed above. While Mirkin et al also teach the detection of probes in high molecular weight DNA (page 24, lines 18-23), Mirkin et al are silent with respect to metaphase chromosomes.

However, Klinger et al teach hybridization of probes to metaphase spreads of chromosomes (column 4, lines 23-27) with the added benefit of diagnosing chromosomal aneuploidies (column 2, lines 60-63).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Mirkin et al with the metaphase chromosome spread as taught by Klinger et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in diagnosing chromosomal aneuploidies as explicitly taught by Klinger et al (column 2, lines 60-63).

11. Claims 1, 21, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Lebo (U.S. Patent No. 5,665,540, issued 9 September 1997).

Regarding claim 21, the method of claim 1 is discussed above. While Mirkin et al also teach the detection of probes in high molecular weight DNA (page 24, lines 18-23), Mirkin et al are silent with respect to interphase nuclei.

However, Lebo teaches the hybridization of probes to interphase nuclei with the added advantage of allowing the counting of adjacent gene copies and detection gene deletion (column 4, lines 38-50).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Mirkin et al with the interphase nuclei as taught by Lebo with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing the counting of adjacent gene copies and detection gene deletion as explicitly taught by Lebo (column 4, lines 38-50).

Regarding claim 22, the method of claim 1 is discussed above. While Mirkin et al also teach the method wherein the target is a polynucleotide is located in a tissue (page 24, lines 18-20), Mirkin et al are silent with respect to fixed tissues.

However, However, Lebo teaches the hybridization of probes to cells that have been fixed (e.g., column 16, Example I) with the added advantage that fixing cells to slides minimizes false negative results (column 3, lines 17- 22).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method of detection in cells as taught by Mirkin et al with the fixed cells as taught by Lebo with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in minimization of false negative results as explicitly taught by Lebo (column 3, lines 17-22).

12. Claims 1, 23, and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Bruchez et al (Science, vol. 281, pages 2013-2016 (1998)).

Regarding claim 23, the method of claim 1 is discussed above. While Mirkin et al also teach the detection of color changes on the substrate (page 83, lines 18-20 and Figure 13A, last step), Mirkin et al are silent with respect to applying a light source and detecting fluorescence emission.

However, Bruchez et al teach the use of semiconductor nanocrystals and fluorescent biological labels (Title), wherein a light source is applied to the nanocrystal and fluorescence emissions from bound probe-associated nanoparticles are detected (Figure 3) with the added advantage that the fluorescence emission of the nanoparticles is clearly spectrally resolved to the eye (page 2015, column 2, paragraph 1).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising the detection of color changes as taught by Mirkin et al with the detection of fluorescence emission as taught by Bruchez et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in clear optical spectral resolution as explicitly taught by Bruchez et al (page 2015, column 2, paragraph 1).

Regarding claim 26, the method of claim 1 is discussed above. While Mirkin et al teach semiconductor nanoparticles (page 19, lines 24-34), Mirkin et al do not teach shells.

However, Bruchez et al teach the use of semiconductor nanocrystals and fluorescent biological labels (Title), wherein the nanocrystal comprises a shell with the added advantage that the shell prevents photochemical degradation of the nanocrystal (page 2014, column 2, paragraph 2).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising the semiconductor nanoparticles as taught by Mirkin et al with the shells as taught by Bruchez et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in prevention of photochemical degradation of the nanocrystal as explicitly taught by Bruchez et al (page 2014, column 2, paragraph 2).

Regarding claim 27, the method of claim 26 is discussed above. Bruchez et al also teach the shell is CdS (page 2014, column 3, paragraph 2).

13. Claims 1 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Kohne (U.S. Patent No. 5,612,183, issued 18 March 1997).

Regarding claim 29, the method of claim 1 is discussed above. Mirkin et al are silent with respect to determining the amount of the probe present in the sample.

However, Kohne teaches a method of hybridizing nucleic acids that determines the amount of probe in a sample (i.e., a method of determining the degree of and quantitating nucleic acid hybridization, Abstract) with the added advantage that the quantitation allows detection of the sensitivity of organisms to antimicrobial agents (column 12, lines 17-33).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising the detection as taught by Mirkin et al with determining the amount of probe present as taught by Kohne with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing detection of the sensitivity of organisms to antimicrobial agents as explicitly taught by Kohne (column 12, lines 17-33).

14. Claims 1, 33-34, and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997).

Regarding claim 33, the method of claim 1 is discussed above. Mirkin et al also teach a plurality of different targets attached to the substrate and each of the different targets preferentially binds a different probe polynucleotide (e.g., a plurality of oligonucleotides are provided in an array to detect multiple different nucleic acids; page 40, line 32-page 41, line 11). Mirkin et al does not teach separate determination of each binding event.

However, Pinkel et al teach a method of assaying samples for probes (e.g., using a biosensor array to detect nucleic acid binding complexes, Abstract) wherein each binding event is separately determined (e.g., simultaneous assaying of binding components of a test sample are done on by discretely detection at individual locations [i.e., bundles of fibers]; Abstract) with the added benefit that the discrete addressing assists in rapid sample identification (Abstract).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising the detection as taught by Mirkin et al with separately determined detection as taught by Pinkel et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in rapid sample identification as explicitly taught by Pinkel et al (Abstract).

Regarding claim 34, the method of claim 33 is discussed above. Pinkel et al also teach the binding of each different probe polynucleotide to its corresponding different target can be separately determined through a different identified position at which each different target is attached to the substrate (e.g., the substrate comprises fibers to which the nucleic acids [i.e., binding partners] are attached, and each fiber is uniquely identified and discretely addressed to detectors; Abstract).

Regarding claim 36, the method of claim 33 is discussed above. Pinkel et al also teach the hybridization of each different probe polynucleotide to its corresponding different target can be separately determined by the conditions under which it hybridizes (e.g., hybridization occurs under defined stringency conditions; column 6, lines 16-30).

Regarding claim 37, the method of claim 33 is discussed above. Mirkin et al also teach the method wherein each different probe polynucleotide is bound to a different tag-binding conjugate which comprises a semiconductor nanocrystal the same as the first semiconductor nanocrystal (e.g., each spot in the array is assayed with oligonucleotide nanoparticle conjugates

[page 41, lines 1-11], wherein the nanoparticle is a semiconductor nanoparticle [page 19, lines 24-34], and wherein the oligonucleotide nanoparticle conjugates are attached to the same type of particle (e.g., Example 10 and Figure 13a). The broad limitation "a semiconductor nanocrystal the same as the first semiconductor nanocrystal" is interpreted in the instant claim to mean that the nanocrystals are all composed of the same materials (e.g., Example 10).

Regarding claim 38, the method of claim 33 is discussed above. Mirkin et al also teach the method wherein each different probe polynucleotide is bound to a different tag-binding conjugate which comprises a different semiconductor nanocrystal (e.g., each spot in the array is assayed with oligonucleotide nanoparticle conjugates [page 41, lines 1-11], wherein the nanoparticle is a semiconductor nanoparticle [page 19, lines 24-34], and wherein the oligonucleotide nanoparticle conjugates are attached to the same type of particle (e.g., Example 10 and Figure 13a). The broad limitation "a different semiconductor nanocrystal" is interpreted in the instant claim to mean the tag-binding conjugates are each bound to a different (i.e., physically distinct) particle (e.g., Figure 13a).

15. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) and Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) as applied to claim 33 above, and further in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999.

Regarding claim 35, the method of claim 33 is discussed above. While Mirkin et al teach the binding of each different probe polynucleotide to its corresponding different target (e.g., a plurality of oligonucleotides are provided in an array to detect multiple different nucleic acids; page 40, line 32-page 41, line 11) and Pinkel et al teach each binding event is separately determined (e.g., simultaneous assaying of binding components of a test sample are done on by discretely detection at individual locations [i.e., bundles of fibers]; Abstract), neither Mirkin et al

nor Pinkel et al teach each conjugate comprises different semiconductor nanocrystals with different fluorescence characteristics.

However, Weiss et al teach the use of semiconductor nanocrystals attached to probes (i.e., affinity molecules) to determine the presence of a detectable substance in a material (Abstract), wherein the probes (i.e., affinity molecules) are nucleic acids (column 6, lines 50-67) and wherein a plurality of differently colored semiconductor probes each having different semiconductor nanocrystals are used with the added benefit of allowing simultaneous detection of a plurality of detectable substances without overlap (column 6, lines 35-47).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Mirkin et al and Pinkel et al with different nanocrystals as taught by Weiss et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing simultaneous detection of a plurality of detectable substances without overlap as explicitly taught by Weiss et al (column 6, lines 35-47).

Conclusion

1. No claim is allowed.

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571) 272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert T. Crow
Examiner
Art Unit 1634

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